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HEAD AND NECK

Repeatedly recurring pleomorphic adenoma: a therapeutic challenge

Adenoma pleomorfo plurirecidivante: una sfida terapeutica

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SUMMARY

Pleomorphic adenoma (PA) is the most common tumour of the salivary glands, and can recur even after proper surgery. The extent and timing of surgery for recurrent tumours remains controversial, and multiple recurrences pose a special challenge. We evaluated all recurrent PAs (RPAs) treated at the Helsinki University Hospital through 2004-2013 focusing on patients with multiple recurrences. Follow-up data were obtained until January 2018. Of the 47 patients, 70% were women and the median age was 33.5 years. Most of the RPAs were located in the parotid gland (87%), and six (13%) in the submandibular gland. One-third (17/47) of tumours had been primarily excised. This patient population experienced 75 recurrent events in total with two or more recurrences in 14 patients (30%). The time interval between recurrences shortened after each recurrent event and the tumour was more likely to be multifocal. At the end of the follow-up period, 15% had recurrent disease and malignant transformation had occurred in 6%. Treatment for PA and RPA is challenging and requires centralised management. Patients with RPA are often young and recurrences may cause lifelong morbidity, especially when the tumour recurs repeatedly. The utilisation and timing of postoperative radiotherapy needs to be discussed as well as the potential risk for malignant transformation in this patient population.

KEY WORDS: Salivary gland • Pleomorphic adenoma • Adenoma • Treatment • Outcome

RIASSUNTO

L'adenoma pleomorfo è il tumore più frequente delle ghiandole salivari. È caratterizzato da un elevato rischio di recidiva anche dopo un'accurata chirurgia. L'estensione ed il corretto timing della chirurgia è controverso sopratutto nei casi di tumori plurirecidivanti. In questo lavoro abbiamo valutato tutti i casi di adenoma pleomorfo plurirecidivante (RPAs) trattati presso l'Helsinki University Hospital dal 2004 al 2013. I dati di follow-up sono stati raccolti sino al gennaio 2018. Dei 47 pazienti considerati, 70% erano donne con un'età media di 33,5 anni. La maggior parte dei RPAs erano localizzati a livello della ghiandola parotide (87%), sei (13%) a livello delle ghiandole sottomandibolari. Un terzo (17/47) dei tumori sono stati rimossi chirurgicamente. All'interno di questa popolazione di pazienti sono stati documentati 75 eventi di recidiva di malattia, 14 pazienti (30%) hanno avuto 2 o più recidive. L'intervallo di tempo intercorso fra le singole recidive si è gradualmente accorciato con un incremento progressivo del rischio che il tumore si ripresentasse a livello multifocale. Al termine del periodo di follow up, 15% dei pazienti hanno avuto recidiva di malattia, nel 6% si è verificata la degenerazione maligna del tumore. Il trattamento dell'adenoma pleomorfo plurirecidivante rappresenta una sfida terapeutica e richiede un management centralizzato. I pazienti affetti da RPA sono spesso di giovane età, il trattamento delle forme plurirecidivanti è gravato da un'elevata morbidità negli anni. L'impiego ed il timing di un'eventuale radioterapia post operatoria nonchè il rischio di degenerazione maligna sono parametri da prendere in considerazione per una corretta gestione multidisciplinare dei RPA.

PAROLE CHIAVE: *Ghiandole salivari • Adenoma pleomorfo • Adenoma • Trattamento • Risultati*

Introduction

Pleomorphic adenoma (PA) is the most common tumour of the salivary glands with an incidence rate between 4.2-4.9/100,000 person-years [1 2]. Recurrences occur despite proper surgery. Treatment of recurrent PA (RPA) remains a challenge, and some tumours may even be incurable. The occurrence of satellite nodules and pseudopodia of PA may occur due to incomplete capsule of the tumour [3], which may lead to residual disease, especially after limited surgery such as enucleation. Rupture of the capsule results in spillage of tumour cells and increases the risk for recurrences 14- to 21-fold [4 5]. Also, positive surgical margins increase the risk of recurrence, but in these circumstances the term residual disease instead of recurrence may be more accurate. In close proximity of a tumour of the parotid gland to the facial nerve

(FN), the tumour needs to be dissected extracapsularly [6], which may result in recurrences even after proper superficial parotidectomy (SP). Since not all tumours with rupture of the tumour capsule recur, and some recur after adequate surgery, the causes for RPA seem multifactorial.

Some studies report that age [7 8] and gender [8] have an influence on the potential of PA to recur, but others show no influence [4 5 9]. Controversies exist between the risk for RPA and cellular composition of PA primarily. The most likely reasons for RPA to date are rupture of the capsule leading to tumour spillage and positive surgical margins [4], although as pointed by Colella et al. [10], studies supporting this conception are limited. The abandonment of enucleation and preferring more extended surgery seem to have led to a dramatically decreased recurrence rate of PA from up to 45% to as low as 1% [5 6 10]. Favouring extracapsular dissection (ECD) nowadays in parotid PA over routine SP does not result in a higher recurrence rate [6 10], but does minimise the risk for FN dysfunction and other complications [11]. Furthermore, a recent meta-analysis on parotid PAs reported that the recurrence rate after ECD was half that after SP in experienced hands [10].

The aim of the present study was to evaluate RPA treated at our institution over a 10-year period. We report the treatment and outcome of 47 consecutive patients and discuss the reasons for recurrences and treatment of RPA with special focus on multiple recurrences.

Patients and methods

Patients with any recurrence of PA diagnosed at the Helsinki University Hospital between January 1, 2004 and January 1, 2014 were included. We collected information on patient demographics, clinical history, diagnostics, clinical and pathological features of tumours, recurrences and their treatment, FN function and follow-up data. To gather further follow-up data after diagnosis of RPA, all events until January 2018 were recorded. This study was approved by the institutional Research Ethics Board (192/13/03/02/16) and study permission was granted.

During the study inclusion period, 47 patients with RPA were diagnosed. During the same period, 796 patients were operated for a benign salivary gland PA, including the RPAs, at our institution.

We included also RPA with malignant changes, i.e. CXPA. An additional search revealed 14 patients with CXPA during the period, but only one had presented with a previously treated PA.

Results

Of the 47 patients, 33 were women (70%) and 14 were men (30%). The median age at time of diagnosis of the primary tumour was 33.5 years (range, 10-65). Most of the tumours were located in the parotid gland (n = 41; 87%), and six (13%) in the submandibular gland. We found no RPAs of the minor salivary glands. Altogether, 75 recurrent events occurred in this patient population. Of all patients, 33 had one recurrence, seven had two, four had three, one had four, one had five and one patient experienced seven recurrences. In 41 patients, the primary surgery had been carried out before the study inclusion period (January 1, 2004) (Fig. 1). Of the recurrent events, 12 occurred before this date, and further recurrences after the study inclusion period were diagnosed in two patients.

Primary tumours and treatment

The initial treatment of the primary tumours was performed during 1969-2009 by various head and neck surgeons. In 23 cases, treatment had been executed at other institutions, even some in other countries (n = 4), limiting available information on the initial phase of treatment.

Of the 41 parotid gland tumours, 38 were initially located in the superficial lobe, two in the deep lobe and one was extended to both lobes. Surgery of parotid gland tumours consisted of removal of the tumour only in 15 patients, superficial or partial parotidectomy in 22 patients and total parotidectomy in three patients. In one patient, surgical data remained unavailable. Of the six patients with a submandibular gland tumour, four had had removal of the gland with the tumour, and two had had limited surgery with a purpose of tumour removal only.

Rupture of the tumour capsule and direct spillage of tumour cells was reported in eight (17%) patients. None of the primary tumours were multifocal.

First recurrence

The median time between primary treatment of the tumour and first recurrence was 10.3 years (mean, 13.3; range, 1.3-39.4). All except one of the 47 patients underwent surgery for the first recurrence. Surgery for 40 parotid gland RPAs consisted of resection of single adenomas in 18 patients (45%), partial or superficial parotidectomy in 15 patients (38%), total parotidectomy in six (15%) and radical surgery in one patient (3%). Surgery for submandibular gland RPA included resections of a single adenoma in two patients, or at least level I B dissection in four.

Rupture of the tumour capsule and direct spillage of tumour cells was reported in four cases (9%). In three cases surgery was non-radical, and these patients had persistent disease at the end of follow-up. On histopathological examination, positive surgical margins were reported in 19 cases (41%), and multifocal disease in 27 cases (59%).

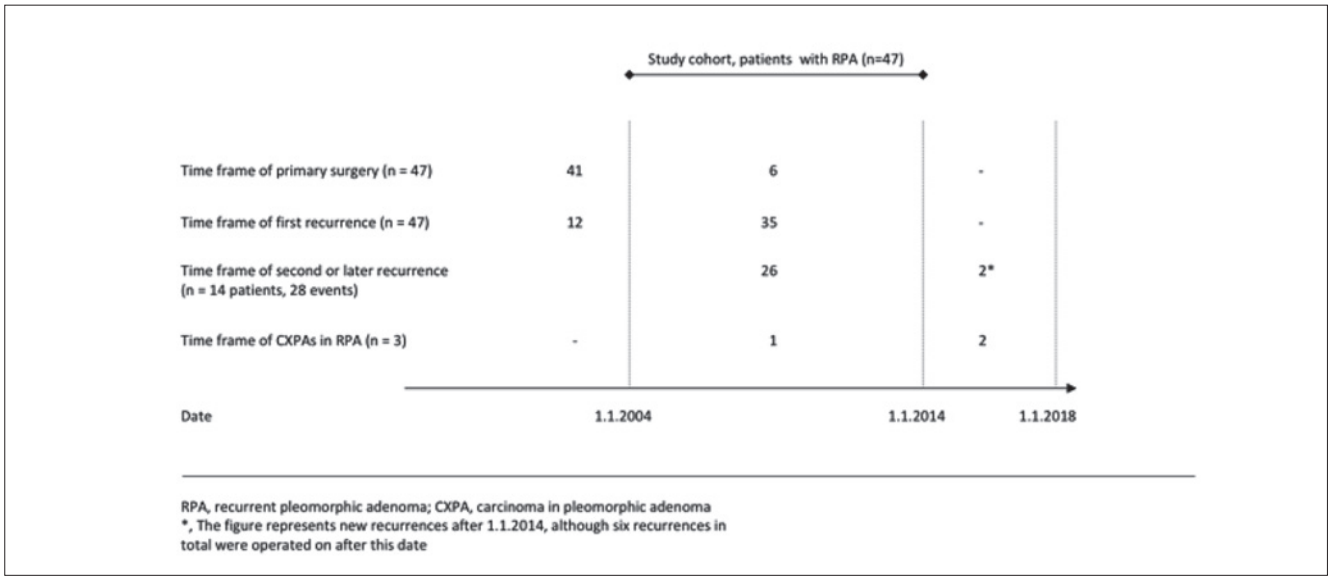

Fig. 1. Time frames of the diagnosis of the primary tumours and recurrences.

Radiotherapy (RT) with 60 Gy was administered in three patients after a benign recurrent tumour, in all after the first recurrence.

Second and later recurrences

The majority (n = 31; 70%) of the patients had a single recurrent event, whereas a second recurrence (i.e two or more recurrent events) occurred in 14 (30%) patients. 11 (79%) emerged in the parotid gland, and three (21%) in the submandibular gland.

Of the 14 patients undergoing additional surgery for second recurrence, rupture of the tumour capsule and direct spillage of tumour cells was reported in four cases (29%). Histopathological examination revealed positive surgical margins in two patients (14%), and multifocal disease in eight cases (57%).

A third recurrence (i.e. three or more recurrent events) was observed in seven patients (15%), six in the parotid gland and one in the submandibular gland. The recurrence was multifocal in five of these patients (71%). Further recurrences occurred in three patients. Their surgery included excision of single adenomas.

The time interval between recurrences shortened after each recurrent event with a median of 5.8 years (mean, 7.5; range, 1.2-20.1) between the first and the second recurrence.

At the end of the follow-up period (January 1, 2018), seven patients presented with recurrent disease: one patient who had been treated with postoperative RT presented with an unchanged parapharyngeal space recurrence within a 3-year follow up. Surgery had been non-radical in three patients with multifocal disease and they had been followed up without further treatment. In the remaining three cases, multiple tumours after repeated recurrences had been followed up and their status had remained almost unchanged for 4-9 years.

Carcinoma ex pleomorphic adenoma

Three patients experienced a carcinoma in their recurrent tumours. In one patient, this occurred in the first recurrence 14 years after the treatment of the primary tumour. The patient had two palpable tumours, which had grown within 3-4 years, but MRI and histology revealed numerous carcinomatous lesions. In the two other patients, multifocal carcinoma was diagnosed in the third recurrent event. These appeared at 20 and 37 years after the treatment of the primary tumour (7 and 16 years after previous recurrences). Fine needle aspiration cytology (FNAC) was taken in two of these patients, and in one patient it was highly suspicious of malignancy and in the other it was slightly suspicious.

Discussion

We had 47 RPA cases, 14 of whom (30%) later experienced further recurrences. During our study period, the rate of recurrences of all PAs operated on at our institution was 6%. However, this does not reflect the true recurrence rate, as many of the tumours had initially been operated on decades ago, and at several other hospitals. Notwithstanding, our results are in line with Valstar et al. [1] and Colella et al. [10]. The latter meta-analysis reported the recurrence rate to vary according to the type of surgery from 1-8%.

Women were more often affected in the present study, and

this has also been shown by others [1 2 12 13]. Andreasen et al. [2] reported in a national study a median age for PA to be over 50 years, and showed a tendency for younger age among patients who experienced recurrences. This tendency was also obvious in the current study.

We and others nowadays favour MRI as the preferred imaging method in RPA [14]. It is superior in detecting multinodularity, but the smallest nodules still remain undetectable [14]. In our series, MRI was used rarely in superficial lesions. Instead, ultrasound (US) and US-guided FNAC was used in many cases. The sensitivity of FNAC for detecting salivary gland neoplasms is generally around 83% [15], and even higher for PA [16 17], and was 67% in the present study (data not shown). Heaton et al. [16] have shown that FNAC combined with MRI can offer highly confident preoperative diagnosis of PA [16]. Of note, Zbären et al. [18] reported that the sensitivity of FNAC to detect CXPA was only 47%, and the malignancy of PA was known preoperatively in only 42% of cases. Therefore, FNAC does not seem to be adequate in defining the eventual malignant nature of a recurrent tumour. In our series, FNAC indicated malignancy correctly, but was obtained in only two of three CXPAs.

Basically, despite the surgical method, all techniques for superficial parotid PA expose the tumour capsule focally [6]. A meta-analysis shows that a rupture of the capsule of the primary tumour and tumour spillage are strongly associated with recurrence [6]. However, rupture of a capsule does not always lead to recurrence, and several reports have shown no association of tumour cell seeding with recurrences [6 13 19]. Dell'Aversana et al. [20] showed that favouring ECD in superficial parotid gland tumours instead of SP seems to decrease possible postoperative complications, but may carry a higher risk for rupture of the capsule and an increase in recurrences, although not all support this conception [6]. In our cohort, surgery for the primary tumour included removal of the tumour only in 36% of cases. Knowledge of tumour biology and education of the appropriate treatment are vital.

In our cohort, tumour spillage after rupture of the capsule of the primary tumour was known only infrequently. Obviously, a structured surgical and histopathological worksheet should be outlined to complete clinically relevant tumour characteristics and possible complications during surgery. The primary treatment of PA should therefore be carefully planned, executed and centralised in experienced centres. Valstar et al. [1] showed that positive resection margins increased the risk for recurrence over fourfold, and Espinosa et al. [13] reported the risk to be even 49 times higher.

Incomplete capsule, capsule penetration, pseudopodia, or satellite tumours are common in PA. Zbären and Stauffer [12] reported these features to be present in 73% of a cohort of 218 tumours. Satellite nodules increase the risk for RPA, as they are observed in 60% of RPAs compared to 10% in non-recurrent tumours [4]. Thus, negative surgical margins do not guarantee successful surgery in terms of tumour recurrence [21]. Satellite nodules seem to be more common in tumours over 4 cm [4 22 23], as they are observed in 33% of such tumours compared to 6-10% in those smaller than 4 cm [22]. We had only two (12%) tumours that were over 4 cm. Delays in treatment may also increase the size of the recurrent tumour and thus increase treatment-related complications [24]. Some studies show that the myxoid histologic subtype of PA with incomplete encapsulation has a higher risk for RPA [12 23] and some show no significance of the cellular subtype [4 13], while another study indicated that the risk appears to be higher in hypercellular tumours [7].

Multinodular tumours and tumours with local excision only are more likely to recur repeatedly [9]. Redaelli de Zinis et al. [9] reported an overall recurrence rate of 33% for second recurrences, reflecting our results (32%). None of their patients with a parotid RPA with a single node recurred. They found that patients with multiple nodules who did not undergo at least SP were at higher risk to recur. In our cohort, after every recurrence, the tumour was more often multifocal and thus complicating the surgical treatment. Thus, limited surgery consisting of resection of single nodules was more often executed in the second recurrence.

Additional surgery for RPA increases the risk for FN paralysis [8 14]. This was also obvious in our patient cohort, but comprehensive data were difficult to extract retrospectively from hospital records. A recent prospective study assessing the complications of parotid gland surgery reported immediate postoperative FN paralysis in 40% of patients when the slightest changes were taken into account [25], although nerve monitoring and the use of microscope decrease the risk [26]. A review by Witt et al. [14] revealed that after surgery of a parotid gland RPA, temporary FN injury occurred in 90-100%, and permanent FN injury in 11-40% of cases. This highlights the importance of adequate treatment of RPA in the first recurrent event.

Postoperative RT should be discussed in cases of PA with negative prognostic factors [27]. In some cases RT is an option to preserve FN function [28], and some have administered RT for PA with close or positive surgical margins [29 30] with good local control. Witt et al. [14] summarised local tumour control after postoperative RT and it seems that RT improves treatment outcomes in patients with multinodular tumours with several recurrences. RT should be administered after surgery: Douglas et al. [31]

reported postoperative RT to result in a 100% 15-year locoregional control among patients with microscopic disease compared to 76% for patients with macroscopic disease. Many studies included only a few patients who received RT. Conclusions on indications of RT are thus hard to outline. Furthermore, it is unclear after which recurrent event is RT beneficial and should be recommended. Also, since patients usually present tumours at an early age, the side effects of RT need to be considered, and whether RT can induce the growth of other nodules in the future. We had only three patients who received RT for benign RPA. Furthermore, half of the patients who had a second recurrence developed further recurrences, and even malignancy. Thus, we might speculate that more extensive utilisation of postoperative RT could have deferred further recurrences. Based on the results from our series and the current literature, postoperative RT seems warranted in multifocal recurrent disease and in patients for whom additional surgery would most likely cause significant morbidity. We had several patients who had been followed up after detection of repeated recurrence. Among these, additional surgery was considered impossible without sacrifice of the facial nerve, and RT was not optimal because of macroscopic disease. It is noteworthy that even 6% of patients in our series developed CXPA and patients in follow-up are still in high risk of developing a malignancy. This clinical dilemma supports administration of postoperative RT for RPA.

The majority of CXPA are diagnosed as de novo cases [2,18], although PA may undergo malignant transformation with an increased risk over time [14]. If PA is left untreated, recent studies show that the risk for malignant transformation is generally considered to be around 1.1-1.7% [1,2]. RPA gains potential for malignant transformation after repeated recurrences [14,21]. On the other hand, 12% of CXPA have been shown in patients with a previous operation for PA, and the rate of malignant transformation in RPA has been reported around 3-4% [32], reflecting the results of the present study. As Suh et al. [21] show, younger patients are at higher risk for developing recurrences and therefore malignancies in the future.

The causes which lead to subsequent recurrences occur most likely at the time of the primary surgery [27], but the subsequent recurrences become clinically evident later. Therefore, we can contemplate that treatment of RPA had been inadequate in several cases. The mean time interval from the treatment of the primary tumour to diagnosis of first recurrence was as long as 12 years in the present study. Another study also reported that tumours commonly recur more than 10 years after initial surgery [19]. Zbären et al. [7] reported a mean nine-year interval between the first and second recurrence, reflecting the mean 7.5-year interval in the present study, but a recent study reported a much shorter interval of two years [1]. The time interval between recurrences in our cohort, however, shortened after every recurrence, as reported in another study [21]. We can speculate whether a follow-up period instead of immediate surgery after detection of RPA would be warranted. This could reveal whether there will appear several additional lesions since MRI fails to show all small nodules. Thus, the extent of surgery could be planned more adequately to avoid multiple surgeries. Significant morbidity after additional surgery probably limits the desire to proceed with more radical surgery among young patients.

Conclusions

Treatment for PA, and especially RPA, is challenging, and surgery of salivary gland tumours thus needs to be centralised. Patients with RPA are often young and recurrences may cause lifelong morbidity, especially in cases with multiple recurrences. Thus, in some cases, follow-up instead of additional surgery might be an option. The role of RT in the management of RPA needs consideration as the risk for malignant transformation is significant. Future research is required to develop new follow-up methods and management options for RPA in order to avoid further recurrences.

Conflict of interest statement

None declared.

References

1 Valstar MH, de Ridder M, van den Broek EC, et al. *Salivary gland pleomorphic adenoma in the Netherlands: a nationwide observational study of primary tumor incidence, malignant transformation, recurrence, and risk factors for recurrence.* Oral Oncol 2017;66:93-9.

2 Andreasen S, Therkildsen MH, Bjorndal K, et al. *Pleomorphic adenoma of the parotid gland 1985-2010: a Danish nationwide study of incidence, recurrence rate, and malignant transformation.* Head Neck 2016;38(Suppl 1):1364-9.

3 Zbaren P, Vander Poorten V, Witt RL, et al. *Pleomorphic adenoma of the parotid: formal parotidectomy or limited surgery?* Am J Surg 2013;205:109-18.

4 Park GC, Cho KJ, Kang J, et al. *Relationship between histopathology of pleomorphic adenoma in the parotid gland and recurrence after superficial parotidectomy.* J Surg Oncol 2012;106:942-6.

5 Riad MA, Abdel-Rahman H, Ezzat WF, et al. *Variables related to recurrence of pleomorphic adenomas: outcome of parotid surgery in 182 cases.* Laryngoscope 2011;121:1467-72.

6 Witt RL. *The significance of the margin in parotid surgery for pleomorphic adenoma.* Laryngoscope 2002;112:2141-54.

7 Zbaren P, Tschumi I, Nuyens M, et al. *Recurrent pleomorphic adenoma of the parotid gland.* Am J Surg 2005;189:203-7.

8 Wittekindt C, Streubel K, Arnold G, et al. *Recurrent pleomorphic adenoma of the parotid gland: analysis of 108 consecutive patients.* Head Neck 2007;29:822-8.

9 Redaelli de Zinis LO, Piccioni M, Antonelli AR, et al. *Management and prognostic factors of recurrent pleomorphic adenoma of the parotid gland: personal experience and review of the literature.* Eur Arch Otorhinolaryngol 2008;265:447-52.

10 Colella G, Cannavale R, Chiodini P. *Meta-analysis of surgical approaches to the treatment of parotid pleomorphic adenomas and recurrence rates.* J Craniomaxillofac Surg 2015;43:738-45.

11 Foresta E, Torroni A, Di Nardo F, et al. *Pleomorphic adenoma and benign parotid tumors: extracapsular dissection vs superficial parotidectomy - review of literature and meta-analysis.* Oral Surg Oral Med Oral Pathol Oral Radiol 2014;117:663-76.

12 Zbaren P, Stauffer E. *Pleomorphic adenoma of the parotid gland: histopathologic analysis of the capsular characteristics of 218 tumors.* Head Neck 2007;29:751-7.

13 Espinosa CA, Fernandez-Valle A, Lequerica-Fernandez P, et al. *Clinicopathologic and surgical study of pleomorphic adenoma of the parotid gland: analysis of risk factors for recurrence and facial nerve dysfunction.* J Oral Maxillofac Surg 2018;76:347-54.

14 Witt RL, Eisele DW, Morton RP, et al. *Etiology and management of recurrent parotid pleomorphic adenoma.* Laryngoscope 2015;125:888-93.

15 Christensen RK, Bjorndal K, Godballe C, et al. *Value of fine-needle aspiration biopsy of salivary gland lesions.* Head Neck 2010;32:104-8.

16 Heaton CM, Chazen JL, van Zante A, et al. *Pleomorphic adenoma of the major salivary glands: diagnostic utility of FNAB and MRI.* Laryngoscope 2013;123:3056-60.

17 Atula T, Panigrahi J, Tarkkanen J, et al. *Preoperative evaluation and surgical planning of submandibular gland tumors.* Head Neck 2017;39:1071-7.

18 Zbaren P, Zbaren S, Caversaccio MD, et al. *Carcinoma ex pleomorphic adenoma: diagnostic difficulty and outcome.* Otolaryngol Head Neck Surg 2008;138:601-5.

19 Natvig K, Soberg R. *Relationship of intraoperative rupture of pleomorphic adenomas to recurrence: an 11-25 year follow-up study.* Head Neck 1994;16:213-7.

20 Dell'Aversana Orabona G, Bonavolonta P, Iaconetta G, et al. *Surgical management of benign tumors of the parotid gland: extracapsular dissection versus superficial parotidectomy - our experience in 232 cases*. J Oral Maxillofac Surg 2013;71:410-3.

21 Suh MW, Hah JH, Kwon SK, et al. *Clinical manifestations of recurrent parotid pleomorphic adenoma.* Clin Exp Otorhinolaryngol 2009;2:193-7.

22 Li C, Xu Y, Zhang C, et al. *Modified partial superficial parotidectomy versus conventional superficial parotidectomy improves treatment of pleomorphic adenoma of the parotid gland.* Am J Surg 2014;208:112-8.

23 Dulguerov P, Todic J, Pusztaszeri M, et al. *Why do parotid pleomorphic adenomas recur? A systematic review of pathological and surgical variables.* Front Surg 2017;4:26.

24 Glikson E, Sagiv D, Mansour J, et al. *Recurrent pleomorphic adenoma: is treatment considerably delayed thus affecting surgical morbidity?* Acta Otolaryngol 2018;138:407-10.

25 Ruohoalho J, Makitie AA, Aro K, et al. *Complications after surgery for benign parotid gland neoplasms: a prospective cohort study.* Head Neck 2017;39:170-6.

26 Carta F, Chuchueva N, Gerosa C, et al. *Parotid tumours: clinical and oncologic outcomes after microscope-assisted parotidectomy with intraoperative nerve monitoring.* Acta Otorhinolaryngol Ital 2017;37:375-86.

27 Bradley PJ. *The recurrent pleomorphic adenoma conundrum*. Curr Opin Otolaryngol Head Neck Surg 2018;26:134-41.

28 Becelli R, Morello R, Renzi G, et al. *Recurrent pleomorphic adenoma of the parotid gland: role of neutron radiation therapy.* J Craniofac Surg 2012;23:e449-50.

29 Patel S, Mourad WF, Wang C, et al. *Postoperative radiation therapy for parotid pleomorphic adenoma with close or positive margins: treatment outcomes and toxicities.* Anticancer Res 2014;34:4247-51.

30 Wallace AS, Morris CG, Kirwan JM, et al. *Radiotherapy for pleomorphic adenoma.* Am J Otolaryngol 2013;34:36-40.

31 Douglas JG, Einck J, Austin-Seymour M, et al. *Neutron radiotherapy for recurrent pleomorphic adenomas of major salivary glands.* Head Neck 2001;23:1037-42.

32 Abu-Ghanem Y, Mizrachi A, Popovtzer A, et al. *Recurrent pleomorphic adenoma of the parotid gland: institutional experience and review of the literature.* J Surg Oncol 2016;114:714-8.

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